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Rhodium-Catalysed Coupling of Allylic, Homoallylic, and Bishomoallylic Alcohols with Aldehydes and *N*-Tosylimines: Insights into the Mechanism

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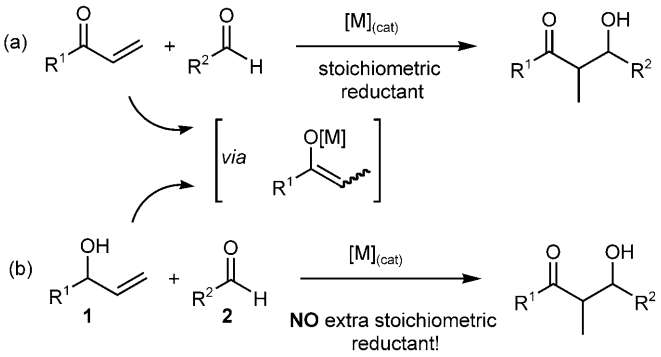
Abstract: The isomerisation of alkenols followed by reaction with aldehydes or *N*-tosylimines catalysed by rhodium complexes has been studied. The catalytically active rhodium complex is formed *in situ* from commercially available (cyclooctadiene)rhodium(I) chloride dimer $[Rh(COD)Cl]_2$. The tandem process affords aldol and Mannich-type products in excellent yields. The key to the success of the coupling reaction is the activation of the catalysts by reaction with postassium *tert*-butoxide (*t*-BuOK), which promotes a catalytic cycle *via* alkoxides rather than rhodium hydrides. This mechanism minimises the formation of unwanted by-products. The mechanism has been studied by ^{1}H NMR spectroscopy and deuterium labelling experiments.

Keywords: aldehydes; allylic alcohols; isomerization; rhodium; *N*-tosylmines

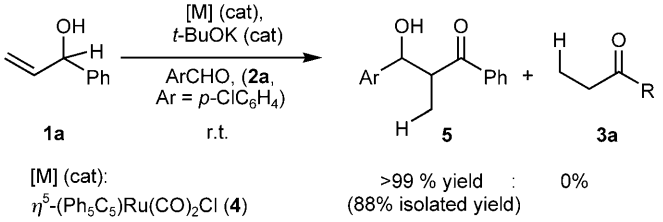
Introduction

Enolates are undoubtedly very important intermediates in synthetic organic chemistry for the formation of C–C bonds.[1] Despite the numerous applications where enolates are key intermediates, the development of new strategies to generate enolates in a regioselective manner is rare. The most common way to form enolates is by treatment of carbonyl compounds with base. Although regioselective deprotonation of unsymmetrical ketones may be achieved by using kinetically or thermodynamically controlled reaction conditions, in those cases where both groups at the α-position of the ketone functionality have similar degrees of substitution, a mixture of enolates is usually produced. In these instances, other approaches may be used. For example, regioselective enolate formation can be achieved by stoichiometric reduction of enones using lithium and liquid ammonia.[2] Much more attractive is the *in situ* catalytic formation of enolates mediated by transition metal complexes using stoichiometric reductants, such as silanes,[3,4] hydrogen,[5] diethylzinc[6] or aldehydes[7] [Scheme 1 (a)]. The enolate intermediates can be trapped by electrophiles present in the reaction mixture. In the case of using aldehydes, aldol products are produced through an overall reductive aldol tranformation.[3–7] Another very attractive method to regioselectivily produce enolates is the isomerisation of allylic alcohols (**1**) catalysed by transition metal complexes [Scheme 1 (b)].[8] In this case, a stoichiometric reductant is not required since the enolate is formed from the starting allylic alcohol in an internal redox process.



Scheme 1. Transition metal-catalysed regioselective aldol formation *via* (a) reductive aldol from enones, and (b) tandem isomerisation/aldol reaction from allylic alcohols.

The two methods (Scheme 1) offer several advantages over the classical approaches in terms of regioselectivity and atom-economy.[9] While great achievements have been reached in the reductive aldol ap-



Scheme 2. Coupling of allylic alcohols and aldehydes catalysed by $[\eta^5\text{-}(Ph_5Cp)Ru(CO)_2Cl]$ (**4**).

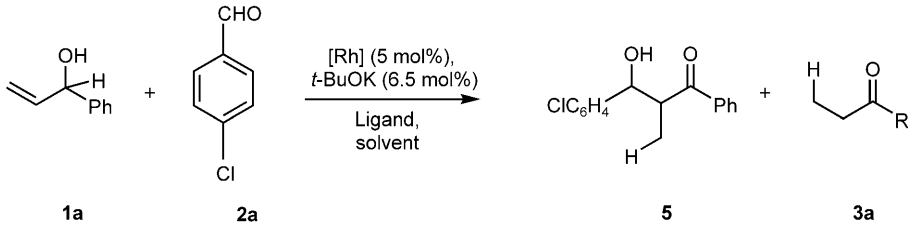
proach where aldols can be produced with high diastereo- and enantioselectivity,[5,3d,h,j–l] the tandem isomerisation/aldolisation of allylic alcohols [Scheme 1 (b)] still remains in its infancy.[10,11,12]

A major problem encountered in the transition metal-catalysed coupling between allylic alcohols (**1**) and aldehydes (**2**) to produce aldols has been the low efficiency of the reaction due to the formation of unwanted ketone by-products (**3** in Scheme 2) formed from the corresponding allylic alcohols in an internal redox process. Li et al. used $Ru(PPh_3)_3Cl_2$ in toluene/H_2O mixtures at 100 °C to obtain aldols in moderate yields (27–72%).[10a] When they used aromatic allylic alcohols, such as α-vinylbenzyl alcohol (**1a**),[10b] propiophenone (**3a**) became the major product. The yield of the aldol products dramatically increased in the presence of $In(OAc)_3$.[10b] They also found that in an ionic liquid, the reactions proceeded well at 90 °C.[10c–d] Grée et al. used $Ru(PPh_3)_3HCl$ to produce aldols in up to 72% yield and in short reaction times (<2 h).[11a] However, under such conditions, ketones **3** were formed (5–52%). They have also used Fe and Ni complexes.[11b–e] In the former case, small amounts of regioisomeric aldols were produced. Very good results were obtained with Ni complexes with Mg salts as co-catalysts; aldol products were formed in high yields together with small amounts of ketones **3** (2–15%). During our search for a catalytic system that would perform the isomerisation/aldol domino process with the highest possible atom economy, we found that the ruthenium complex $[\eta^5\text{-}(Ph_5C_5)Ru(CO)_2Cl]$ (**4**) catalyses the transformation of allylic alcohols into aldols in very high yields at room temperature, and the formation of unwanted ketone by-products (**3**) is completely suppressed (Scheme 2).[12]

Despite the excellent results obtained with Ru complex **4**, the current limitations of the system are that **4** is costly to make, and modification of the catalyst structure, for example, changing the ligands, is not straightforward. For these reasons, we planned to develop a tandem transformation using transition metal complexes which can be prepared *in situ* from commercially available reagents. A key aspect to the success of the transformation shown in Scheme 2 is the activation of **4** using *t*-BuOK. As a result, a ruthenium *tert*-butoxide is produced, which is the active catalytic species. We first tried to use commercially available Ru chloride complexes, such as $Ru(PPh_3)_3Cl_2$ or $[Ru(p\text{-cymene})Cl_2]_2/PPh_3$, in combination with *t*-BuOK in the coupling of allylic alcohols with aldehydes. However, these catalytic systems afforded aldol products with very low efficiency, and the amount of ketone by-product (**3**) produced made this approach of no practical use in a total synthesis.[12] The Rh-catalysed reaction of allylic alcohols with aldehydes was first reported by Gree et al.[11a] Although total regioselectivity was obtained, the coupling proceeded in moderate yield and isomerisation of the allylic alcohol (1-octen-3-ol) to the corresponding ketone (3-octanone) occurred in yields in the range of 19–37%. They used $Rh(PPh_3)_3H$ as the catalyst, which was generated *in situ* from Wilkinson's catalyst (**6**) upon treatment with *n*-BuLi. We envisioned that the activation of commercially available Rh chloride complexes could also be performed with *t*-BuOK, and that if the precatalyst is a Rh alkoxide rather than a Rh hydride, the efficiency of the coupling reaction could be improved. Here we report a very efficient coupling of allylic alcohols and other alkenols with aldehydes or *N*-tosylimines catalysed by commercially available Rh chloride complexes activated by *t*-BuOK. Mechanistic investigations are also presented.

Results and Discussion

First, we tested Wilkinson's complex (**6**) in combination with *t*-BuOK as the catalyst system for the coupling between allylic alcohols and aldehydes (Scheme 3, Table 1). At room temperature and in toluene, complex **6** afforded aldol **5**, albeit in only 49%



Scheme 3. Rh-catalysed coupling of allylic alcohols with aldehydes.

Table 1. Screening of reaction conditions.[a]

Entry	Catalyst [5 mol% of Rh]	Phosphine [mol%]	T [°C]	Solvent	t [h]	Conv. [%][b]	**5** [%][b]	**3a** [%][b]
1	$Rh(PPh_3)_3Cl$ (**6**)	–	r.t.	Toluene	5	100	49	46
2	**6**	–	50	Toluene	0.5	100	80	20
3	**6**	–	rt	THF	3	70	47	23
4	**6**	–	40	THF	3	100	90	10
5	**6**	PPh_3 (5)	40	THF	3	100	85	15
6	$[Rh(COD)Cl]_2$ (**7**)	–	40	THF	3	–	–	–
7	**7**	dppe (5)	40	THF	3	9	6	3
8	**7**	dppp (5)	40	THF	3	21	12	9
9	**7**	dppf (5)	40	THF	3	100	77–96	4–23
10	**7**	(±)-BINAP (5)	40	THF	3	70	60	10
11	**7**	PPh_3 (8)	40	THF	2.5	100	97	3
12	**7**	PPh_3 (10)	40	THF	3	100	95	5
13	**7**	$P(p\text{-}OMeC_6H_4)_3$ (7.5)	40	THF	2.5	100	84	16
14	**7**	$P(p\text{-}ClC_6H_4)_3$ (7.5)	40	THF	2.5	54	52	2
15	**7**	$P(2\text{-furyl})_3$ (7.5)	40	THF	1.5	19	14	5
16	**7**	$PMePh_2$ (7.5)	40	THF	1.5	10	7	3
17	**7**	$P(t\text{-}Bu)_3$ (7.5)	40	THF	3	–	–	–
18	$[Rh(MeCN)_2(COD)]\ BF_4$ (**8**)	PPh_3 (7.5)	40	THF	3	<3	–	–
19[d]	**8**	PPh_3 (7.5)	40	THF	3	<80	–	–
20[e]	**7**	PPh_3 (8)	40	THF[c]	2	100	96	4

[a] Unless otherwise stated, *t*-BuOK (0.5 M in THF, 52 μL) was added to a solution of the Rh complex (5 mol%) and the ligand (entries 5, 7–20) in anhydrous THF or toluene (0.5 mL) (dry solvents were obtained using VAC solvent purifier system). The mixture was stirred for 2–3 min before adding a solution of the allylic alcohol **1a** (0.4 mmol) and aldehyde **2a** (0.48 mmol) in THF or toluene (1.5 mL) [allylic alcohol:Rh:*t*-BuOK = 100:5:6.5]. The reaction mixture was introduced in an oil bath at the temperature indicated.

[b] Determined by ^{1}H NMR spectroscopy.

[c] Commercially available THF (puriss p.a., from Sigma–Aldrich). See Supporting Information.

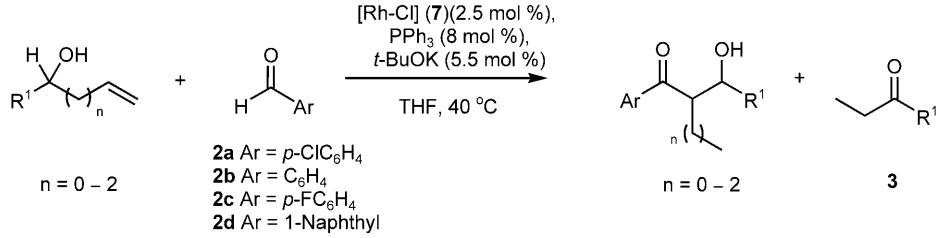
[d] *t*-BuOK was not used. A complex reaction mixture was obtained. Aldol **5** was not detected.

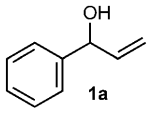
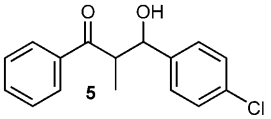
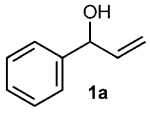
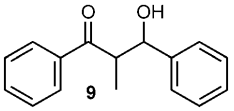
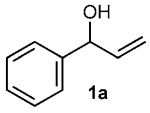
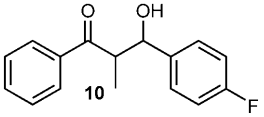
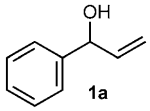
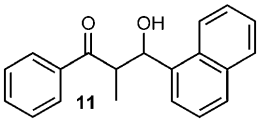
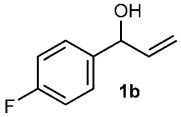
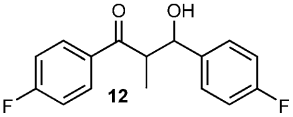
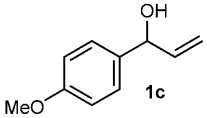
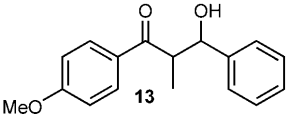
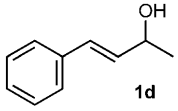
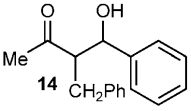
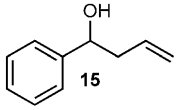
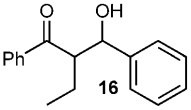
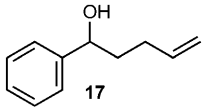
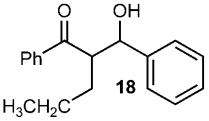
[e] Average of 3 experiments.

yield, and the unwanted isomerisation by-product **3a** was produced in 46% (Table 1, entry 1). The results were improved when the temperature was increased to 50 °C, and aldol **5** could be obtained in 80% yield after only 30 min (Table 1, entry 2). THF (entries 3 and 4) gave better results than toluene. When extra PPh_3 was used, similar results were obtained (entries 4 *vs.* 5). We turned our attention to the use of $[Rh(COD)Cl]_2$ (**7**). In the absence of any ligand, complex **7** did not afford any product (entry 6). The use of bidentate phosphines such as dppe and dppp afforded the product in very low yields (entries 7 and 8). Dppf in combination with **7** gave aldol products in good yields (entry 9). However, variable yields, from 77% to 96%, were obtained. This variation was ascribed to the uncontrolled formation of different Rh complexes when mixing **7** with dppf [e.g., monomeric Rh(I) complexes or Rh(I) coordination polymers]. BINAP did not give better results (entry 10). We were very pleased to see that PPh_3 together with complex **7** gave excellent results. Thus, aldol **5** was produced in 97% yield together with only 3% of **3a** (Table 1, entry 11). Increasing the amount of PPh_3 did not have any effect (entry 11 *vs.* 12). Electron-rich phosphines (entry 13) gave better results than electron-poor ones (entries 14 and 15), and other phosphines such as $PMePh_2$ and $P(t\text{-}Bu)_3$ suppressed the reaction completely or considerably slowed it down (entries 16 and 17). Neither did cationic complexes yield any product in the presence or in the absence of *t*-BuOK (entries 18 and 19, respectively). The reaction is not moisture sensitive and excellent results were obtained in degassed commercially available THF, (see supporting information and Table 1 footnotes).[13] The results obtained were reproducible (entry 20 shows the average of 3 runs) and very similar to those obtained when anhydrous THF was used (entry 20 *vs.* 11). The THF used in all the reactions tested negative for peroxides. Increasing the amount of water by running the reactions in 10:1 THF/H_2O mixtures resulted in a substantial decrease of the reaction rate and lower conversions. The use of other bases (e.g., NaOH) suppressed the reaction or slowed it down.

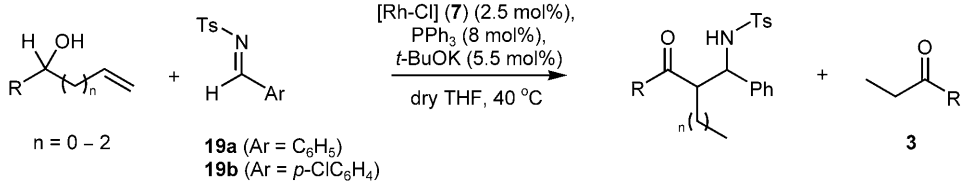
Using the conditions in entry 20 (Table 1), a variety of allylic alcohols were coupled to different aldehydes (Table 2). Allylic alcohol **1a** was coupled to a *p*-chlorobenzaldehyde (**2a**), benzaldehyde (**2b**) and *p*-fluorobenzaldehyde (**2c**) yielding aldols **5**, **9**, and **10** in excellent yields (Table 2, entries 1–3). When more sterically hindered aldehydes were used, such as **2d**,

Table 2. Rh-catalysed coupling of alcohols with aldehydes.[a]



Entry	Alcohol	2	Aldol	*t* [h]	Conv. [%][b]	Yield [%][c]	*syn*:*anti*[b]	3[b] [%]
1	 1a	**2a**	 5	2	100	96[d] (92)[f]	50:50	**3a** (4)[d]
2[e]	 1a	**2b**	 9	2	100	96 (92)	46:54	**3a** (4)
3	 1a	**2c**	 10	2	100	97 (92)[f]	50:50	**3a** (4)
4[g]	 1a	**2d**	 11	1.25	100	85 (78)	56:44	**3a** (15)
5	 1b	**2c**	 12	2	100	94 (91)	40:60	**3b** (6)
6	 1c	**2b**	 13	2.5	100	81 (74)	50:50	**3c** (19)
7	 1d	**2b**	 14	16	92	79[h]	56:44	**3d** (13)
8	 15	**2b**	 16	18	86	73 (66)	36:63	**3g** (13)
9	 17	**2b**	 18	18	86	64[h]	40:60	**3h** (22)[i]

[a] Unless otherwise stated, *t*-BuOK (0.5 M in THF, 45 μL) was added to a solution of dimeric Rh complex **7** (2.5 mol%) and PPh_3 (8 mol%) in THF (0.5 mL, puriss p.a., from Sigma–Aldrich). The mixture was stirred for 2–3 min before adding a solution of the allylic alcohol (0.4 mmol) and aldehyde (0.48 mmol) in THF (1.5 mL) [allylic alcohol:Rh:*t*-BuOK:PPh_3 = 100:5:6.5:8]. The reaction mixture was introduced in an oil bath at 40 °C and stirred for the time indicated.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy, and in parenthesis isolated yield.
[d] Average of three experiments. For results in anhydrous THF see Table 1, entry 11.
[e] In anhydrous THF, 100% conversion, aldol:ketone (%) = 92/8.
[f] Small amounts (5–7%) of regioisomeric aldols were detected. See Supporting Information.
[g] In anhydrous THF, 100% conversion, aldol:ketone (%) = 83/17.
[h] Could not be separated from traces of the starting alcohol. See Supporting Information.
[i] Contains γ,δ-unsaturated ketone (5%).



Scheme 4. Rh-catalysed coupling of allylic alcohols with *N*-tosylimines.

the yields of the aldol products decreased slightly, and the yield of the unwanted ketone **3a** increased (Table 2, entry 4). We turned our attention to other allylic alcohols. Thus, alcohols **1b** and **1c** afforded aldols **12** and **13**, respectively, in excellent yield (Table 2, entries 5 and 6). More interesting is the use of more substituted allylic alcohols such as **1d**, which afforded, in good yield and with total regioselectivity, the coupling product **14** upon reaction with benzaldehyde (entry 7). In contrast to our previous results with Ru complex **4**,[12] that the alcohol and the C=C bond have an allylic relationship is not a requirement for the coupling to occur: the double bond can be placed further away from the alcohol, such as in **15** and **17**, and they also afforded aldols **16** and **18** in good yields (Table 2, entries 8 and 9).

The coupling gave complex reaction mixtures when using electron-rich aldehydes such as *p*-anisaldehyde or 3-tolualdehyde. In these instances, a retroaldol reaction takes place yielding a mixture of different aldol products.

Having established the viability of this reaction, we turned our attention to the use of *N*-tosylimines **19a** and **19b** as the electrophilic partner (Scheme 4, Table 3).[10c] When we searched for optimal reaction conditions, we found that the coupling with *N*-tosylimines requires longer times than that of aldehydes, and that the reaction needs to be performed in dry THF to avoid the formation of aldol products arising from hydrolysis of the imines. A variety of allylic alcohols bearing electron-withdrawing or electron-donating groups yielded Mannich-type products in good to excellent yields (Table 3, entries 1–4). Aliphatic (**1e**) as well as homoallylic alcohols (**15**) were suitable substrates (Table 3, entries 5 and 6).

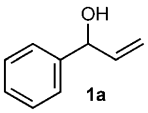
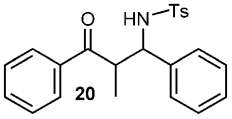
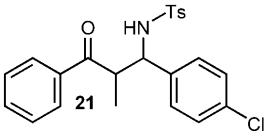
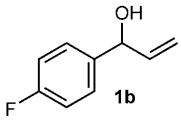
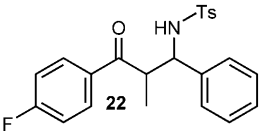
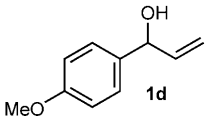
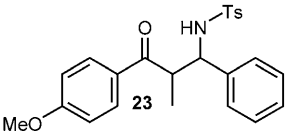
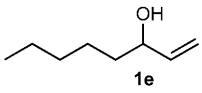
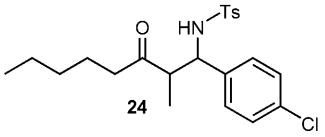
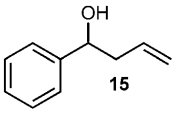
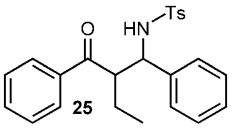
Mechanistic Investigations

The first step in the coupling reaction is the isomerisation of the allylic alcohol to an enol (enolate) intermediate, which in a second step reacts with the aldehyde or *N*-tosylimine forming a new C–C bond. Alternatively, the enol (enolate) tautomerises to the corresponding ketone (yielding the unwanted by-product **3** in the coupling reaction). The isomerisation of the allylic alcohol into the enol(ate) can occur *via* a monohydride or a dihydride mechanism. In the latter, both the O–H and α-C–H hydrogen atoms of the allylic alcohol are transferred to the metal complex yielding a metal dihydride and an α,β-unsaturated ketone.[15] As a result, the hydrogens are scrambled and lose their identity. To distinguish between these two possibilities, the coupling between deuterated allylic alcohol [D_1]**1a** and benzaldehyde was performed. Monodeuterated aldol [D_1]**5**, with the deuterium label exclusively on the methyl group, was obtained (Scheme 5). Thus, a mechanism *via* Rh dihydrides can be ruled out.

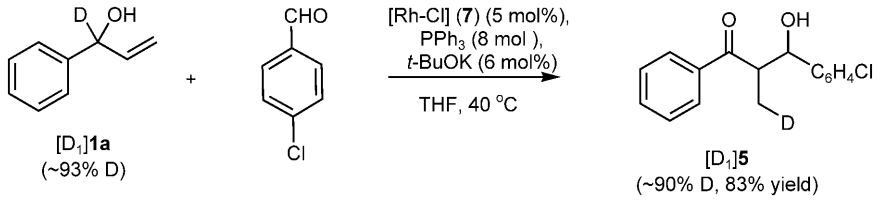
If metal monohydrides are involved, three general mechanisms can be considered (Scheme 6).[8] The first involves alkyl-metal intermediates [path (a) in Scheme 6]. In this case, the catalyst is a metal hydride, either isolated or generated *in situ*. Insertion of the allylic alcohol double bond into the M–H bond, followed by α-C–H bond cleavage leads to an enol and regenerates the metal hydride complex. In the second mechanism [path (b) in Scheme 6], an enol is generated *via* a π-allyl metal hydride complex formed by the oxidative addition of the allylic C–H bond, and would as such involve Rh(III) intermediates. In path (c), the allylic alcohol coordinates to the metal centre forming a metal alkoxide (or a metal-alcohol complex). Following an elimination/insertion pathway, the key metal-enolate intermediate is produced.[14]

We first tried to identify the catalytic species formed when the system Rh (**7**)/PPh_3 is treated with *t*-BuOK. Reaction of dimeric complex **7** with PPh_3 immediately yields the monomeric complex **26** (Scheme 7). The ^{31}P NMR spectrum showed a doublet at 30.9 ppm with a $^1J(^{31}P,^{103}Rh)$ of 152 Hz. The ^1H NMR spectrum was also in agreement with structure **26**, showing the characteristic multiplets in the aromatic region due to coordinated PPh_3, and at higher field the peaks corresponding to coordinated cyclooctadiene (COD). When an excess of PPh_3 was used, the ^{31}P NMR did not show any peak, probably due to a fast exchange of free and coordinated phosphine. The ^1H NMR spectrum showed broad peaks corresponding to the aromatic protons of free and coordinated PPh_3 ligands. The resonances due to coordinated COD were identical to those observed before, when no excess of PPh_3 was present. When *t*-BuOK was added to the NMR tube, complex **26** disappeared, and a new *tert*-butoxide complex was formed by substitution of the Cl ligand by *tert*-butoxide. The new

Table 3. Rh-Catalysed coupling of alcohols with *N*-tosylimines (Sheme 4).[a]

Entry	Alcohol	Imine	Product	*t* [h]	Conv. [%][b]	Yield [%][c]	*syn*:*anti*[b]	**3** [%][b]
1	 **1a**	**19a**	 **20**	14	100	91 (84)	74:26	**3a** (9)
2	**1a**	**19b**	 **21**	14	100	95 (85)	60:40	**3a** (5)
3	 **1b**	**19a**	 **22**	14	100	91 (75)	66:34	**3b** (9)
4[d]	 **1d**	**19a**	 **23**	15	100	81 (73)	70:30	**3d** (19)
5	 **1e**	**19b**	 **24**	15	100	64 (56)	60:40	**3e** (36)
6[d]	 **15**	**19a**	 **25**	15	100	75 (72)	67:33	**3g** (25)

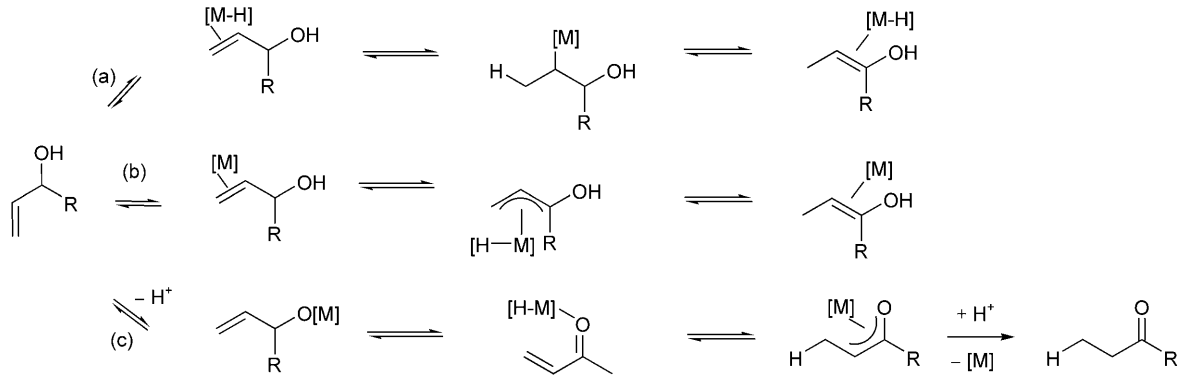
[a] Unless otherwise stated, *t*-BuOK (0.5 M in THF, 45 μL) was added to a solution of dimeric Rh complex **7** (2.5 mol%) and PPh_3 (8 mol%) in dry THF (0.5 mL). The mixture was stirred for 2–3 min before adding a solution of the allylic alcohol (0.4 mmol) and *N*-tosylimine **19a** or **19b** (0.44 mmol) in dry THF (1.5 mL) [allylic alcohol:Rh:*t*-BuOK:PPh_3 = 100:5:6.5:8]. The reaction mixture was introduced in an oil bath at 40 °C and stirred for the time indicated.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy and in parenthesis, isolated yield.
[d] 60 °C.



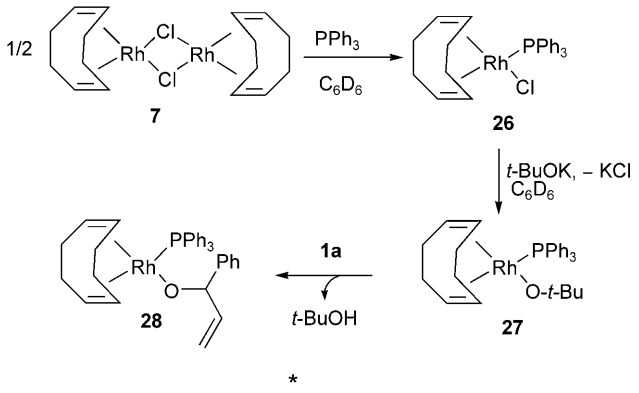
Scheme 5. Coupling of a deuterium-labelled allylic alcohol [D_1]**1a**.

complex (**27**) showed a doublet in the ^{31}P NMR spectrum at 20.5 ppm with a $^1J(^{31}P,^{103}Rh)$ of 162 Hz. The ^{1}H NMR spectrum was also in agreement with the structure proposed for **27**. When 1 equivalent of allylic alcohol **1a** was added to the NMR tube, complex **27** disappeared, and a new complex was formed. This new complex showed splitting of some of the signals corresponding to the olefinic hydrogens of the COD ligand, which indicates that they are diastereotopic (see Supporting Information). This is consistent with coordination of the chiral allylic alcohol **1a** to the Rh complex, forming intermediate **28**. The ^{1}H NMR peaks corresponding to the allylic alkoxide were also in agreement with structure **28**, and differed from those of allylic alcohol **1a**.

Although the NMR studies (Scheme 7) indicate that the alkoxide mechanism [Scheme 6 (c)] may be involved, **28** could undergo β-hydride elimination pro-



Scheme 6. Simplified mechanism of isomerisation of allylic alcohols involving metal monohydride complexes *via*: (a) alkyl-metal intermediates. (b) π-allyl metal hydride intermediates. (c) metal-akoxides.



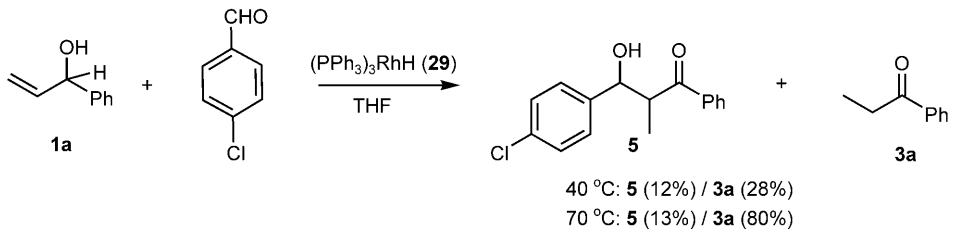
Scheme 7. *In situ* NMR studies.

ducing a Rh hydride, which in turn could be the actual catalytically active species coupling allylic alcohols and aldehydes. To study this possibility, we tried to generate a Rh–H complex upon treatment of a Rh (**7**)/PPh_3 mixture with *n*-BuLi. This catalytic system gave very low yields of aldol **5** after 16 h. However, we were not sure that a Rh–H complex was actually being produced from Rh complex **7**. Hence, we performed a similar experiment using the well known $(PPh_3)_3RhH$ complex (**29**), produced from Wilkinson's catalyst upon treatment with *n*-BuLi (Scheme 8). The coupling of allylic alcohol **1a** with *p*-chlorobenzaldehyde (**2a**) catalysed by $(PPh_3)_3RhH$ (**29**) in THF at 40 °C afforded only 12% of aldol **5** together with 28% of ketone **3a** after > 1 day. The same reaction performed at 70 °C afforded **5** (13%) and ketone **3a** (80%). These results should be compared with the much higher yields of aldol products that we obtained using a [Rh–Cl]/*t*-BuOK catalytic systems (Table 1, entries 4, 11 and 20). Thus, it is unlikely that Rh–H complexes act as the catalysts coupling directly allylic alcohols with aldehydes under our catalytic reaction conditions (Table 2 and Table 3).

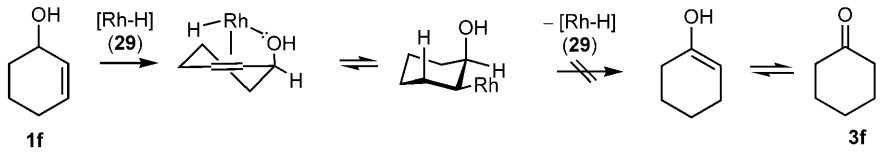
The isomerisation of acyclic allylic alcohols into ketones occurs in excellent yields when Rh hydride complexes are used, as observed by us and others.[16] However, when Rh hydrides are used in the isomerisation of cyclic allylic alcohols, such as 2-cyclohexen-1-ol (**1f**), the corresponding ketone (cyclohexanone, **3f**) is obtained in very low yield.[16] A plausible explanation is that the isomerisation is assisted by coordination of the Rh hydride complex to the alcohol functionality, and in this way, the OH group directs the insertion of the double bond into the Rh–H bond. The intermediate generated cannot undergo *syn* β-hydride elimination to produce the enol (Scheme 9).

Under our reaction conditions, i.e., Rh (**7**)/PPh_3/*t*-BuOK, isomerisation of cyclic allylic alcohol **1f** takes place quantitatively (Scheme 10). This result also indicates that the mechanism of our catalytic system is different from that followed when [Rh–H] complexes are used as the catalyst precursor.

Supported by the mechatisnic studies shown above, we propose a mechanism *via* Rh-alkoxide intermediates, as shown in Scheme 11. The rhodium *tert*-butoxide complex (**27**) can undergo alkoxide exchange with

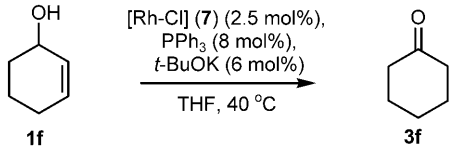


Scheme 8. Rh–H as catalyst in the coupling of allylic alcohols and aldehydes.



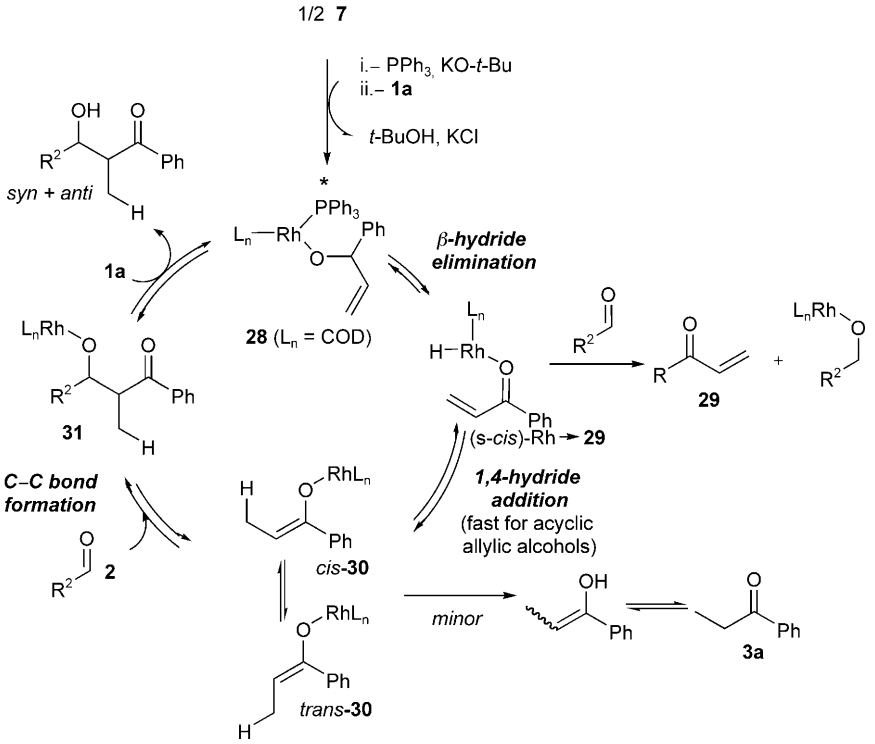
Scheme 9. Rh–H as catalyst in the isomerisation of cyclic allylic alcohol **1f**.

allylic alcohol **1a** to give the new alkoxide **28**, as detected by ^{1}H NMR spectroscopy (see above and Supporting Information). After β-hydride elimination, α,β-unsaturated ketone **29** is formed. In the case of acyclic allylic alcohols, such as **1a**, a fast 1,4-addition of the hydride to the *s*-cis conformation of the α,β-unsaturated ketone yields a Rh-enolate (**30**).[4,5,17] This is supported by the fact that an added aldehyde (**2**) is not reduced to benzyl alcohol by Rh–H species (the ^{1}H NMR spectra of the crude mixtures of the reactions shown in Table 2 showed only traces of benzylic alcohols). On the other hand, for the cyclic allylic alcohol **1f**, an *s*-cis conformation of the cyclohexenone intermediate is impossible to adopt. In the absence of aldehydes, the corresponding Rh(H)→cyclohexenone complex evolves to yield cyclohexanone (*vide supra*, Scheme 10). However, if an aldehyde is present in the reaction mixture, its reduction to benzylic alcohol mediated by an [Rh–H] species becomes a competing pathway, as it has been confirmed (see Supporting Information). This experiment suggests that an s-*cis* conformation of the unsaturated ketone is required for a fast 1,4-hydride addition producing Rh-enolate intermediates (**30**). Enolate **30** then reacts with the aldehyde present in the reaction media affording the aldol product after protonation of alkoxide **31** by an incoming molecule of allylic alcohol.



Scheme 10. Isomerisation of cyclic allylic alcohol **1f** by Rh (**7**)/PPh_3/*t*-BuOK.

For non-allylic alcohols such as **15** and **17**, a mechanism *via* enolates may also be operating. Thus, after β-hydride elimination an enone and a Rh–H are produced. The Rh–H then coordinates to the olefin, and after a number of insertion/β-hydride elimination steps, a conjugated enone is produced. From here, a mechanism similar to that shown in Scheme 11 can explain the formation of the products.



Scheme 11. Proposed mechanism for the Rh-catalysed coupling of acyclic aldehydes with allylic alcohols.

The diastereoselectivity obtained in the aldol reaction is rather low (see Table 2). In our previous work with ruthenium complexes,[12] we observed that at short reaction times, high diastereoselectivity was obtained in favour of the *syn* aldol product (*ca.* 90:10). As the reaction proceeded, the *syn/anti* ratio dropped to *ca.* 80:20. We confirmed that this drop of selectivity is due to a fast epimerisation of the aldol product catalysed by the same Ru complex. In the case of Rh complexes, at short reaction times, the diastereoselectivity is already rather low (e.g., **5** was obtained with *syn/anti* = 51:49 at 25% conversion after 1 h). This low diastereoselectivity can be explained by (i) a Rh-catalysed epimerisation of the final products, (ii) a non-Zimmerman–Traxler-type transition state or (iii) a rapid interconversion of the σ-allyl Rh-enolates **30**. Krische et al. have suggested that the use of a weakly coordinating π-acidic ligand, such as Fur_3P, may promote enhanced stereocontrol by "tightening" the Zimmerman–Traxler-type transition state.[19] When we replaced PPh_3 for Fur_3P, we were able to obtain slightly better diastereoselectivity (e.g., **3** was obtained with *syn/anti* = 60:40 at 12% conversion after 1 h), although very low conversion (19%) was obtained after long reaction times.

Conclusions

In conclusion, we have developed an efficient Rh-catalysed coupling of allylic alcohols with aldehydes and *N*-tosylimines under mild reaction conditions where the formation of ketones (**3**) or other by-products (benzyl alcohols or α,β-unsaturated ketones) is minimised, and aldol or Mannich-type products are obtained in very good yields (up to 97%). Homoallylic- and bishomoallylic alcohols can also be used in the tandem reactions. Commercially available Rh complexes have been employed. Mechanistic investigations indicate that a mechanism *via* metal alkoxides may be involved. We believe this is the key to the success of the tandem process, since when preformed Rh hydrides are used as catalysts, low yields are obtained. Further investigations on the mechanism and future applications of this efficient coupling are under development.

Experimental Section

General Experimental Methods

All reactions were carried out under nitrogen atmosphere. Unless otherwise noted, THF was used as obtained from supplier (Sigma Aldrich, puriss. p.a.). Anhydrous THF and toluene were obtained using VAC solvent purifier system. Flash chromatography was carried out on silica gel 60 (35–70 μm). ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, using a Bruker spectrometer. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ ($\delta_H = 7.26$ and $\delta_C = 77.00$) or in benzene-d_6 ($\delta_H = 7.16$) as internal standards, and coupling constants (J) are given in Hz. High resolution mass spectra (HR-MS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer. The products were characterised by ^1H NMR, ^{13}C NMR, and HR-MS.

General Procedure for the Coupling of Allylic Alcohols with Aldehydes

A freshly prepared solution of *t*-BuOK (45 μL, 0.5 M in THF, 5.5 mol%) was added to a stirred solution of $[Rh(COD)Cl]_2$ (4.9 mg, 0.01 mmol) and PPh_3 (8.4 mg, 0.032 mmol) in degassed THF (0.5 mL, (Sigma Aldrich, puriss. p.a.) *via* syringe. The mixture was stirred at room temperature for 3 min before the addition of the aldehyde (0.48 mmol) and the allylic alcohol (0.4 mmol) in THF (1.5 mL). The flask was immediately introduced in an oil bath at 40 °C, and on completion (monitored by TLC) quenched by absorption on silica. Products were isolated by column chromatography (pentane:EtOAc 10/1) as mixtures of *syn* and *anti* diastereomers.

General Procedure for the Coupling of Allylic Alcohols with *N*-Tosylimines

A freshly prepared solution of *t*-BuOK (45 μL, 0.5 M in THF, 5.5 mol%) was added to a stirred solution of $[Rh(COD)Cl]_2$ (4.9 mg, 0.01 mmol) and PPh_3 (8.4 mg, 0.032 mmol) in dry and degassed THF (0.5 mL) containing MS 3 Å (~10 mg) *via* syringe. The mixture was stirred at room temperature for 3 min before the addition of a solution of the *N*-tosylimine (0.44 mmol) and the allylic alcohol (0.40 mmol) in THF (1.5 mL). The mixture was heated to the appropriate temperature and stirred for the time indicated (see Table 3). Products were isolated by column chromatography (pentane:EtOAc 8/1) as pure *syn* and *anti* diastereomers.

Supporting Information

Characterisation and $^1H/^{13}C$ NMR spectra of **5**, **5**[D_1], **9**–**14**, **16**, **18**, **20**–**28** and spectra of the mechanistic studies are available as Supporting Information.

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